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SOUTHERN DIVISION

ROBERT MERRIWEATHER,

Plaintiff,

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(54) **Anti-angiogene compositions and methods of use**

(57) The present invention provides compositions an anti-angiogenic factor, and a polymeric carrier. Representative examples of anti-angiogenic factors include Anti-invasive Factor, Retinoic acids and derivatives therof, and taxol. Also provided are methods for embolizing blood vessels, and eliminating biliary, urethral, esophageal, and tracheal/bronchial obstructions.

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DescriptionTechnical Field

5 **[0001]** The present invention relates generally to compositions and methods for treating cancer and other angiogenic-dependent diseases, and more specifically, to compositions comprising anti-angiogenic factors and polymeric carriers, stents which have been coated with such compositions, as well as methods for utilizing these stents and compositions.

Background Of The Invention

10 **[0002]** Cancer is the second leading cause of death in the United States, and accounts for over one fifth of the total mortality. Briefly, cancer is characterized by the uncontrolled division of a population of cells which, most typically, leads to the formation of one or more tumors. Although cancer is generally more readily diagnosed than in the past, many forms, even if detected early, are still incurable.

15 **[0003]** A variety of methods are presently utilized to treat cancer, including for example various surgical procedures. If treated with surgery alone, however, many patients (particularly those with certain types of cancer, such as breast, brain, colon and hepatic cancer) will experience recurrence of the cancer. In addition to surgery, many cancers are also treated with a combination of therapies involving cytotoxic chemotherapeutic drugs (e.g., vincristine, vinblastine, cisplatin, methotrexate, 5-FU, etc.) and/or radiation therapy. One difficulty with this approach, however, is that radiotherapeutic 20 and chemotherapeutic agents are toxic to normal tissues, and often create life-threatening side effects. In addition, these approaches often have extremely high failure/remission rates.

25 **[0004]** In addition to surgical, chemo and radiation therapies, others have attempted to utilize an individual's own immune system in order to eliminate cancerous cells. For example, some have suggested the use of bacterial or viral components as adjuvants in order to stimulate the immune system to destroy tumor cells. (See generally "Principles of Cancer Biotherapy," Oldham (ed.), Raven Press, New York, 1987.) Such agents have generally been useful as adjuvants and as nonspecific stimulants in animal tumor models, but have not as of yet proved to be generally effective in humans.

30 **[0005]** Lymphokines have also been utilized in the treatment of cancer. Briefly, lymphokines are secreted by a variety of cells, and generally have an effect on specific cells in the generation of an immune response. Examples of lymphokines include Interleukins (IL)-1, -2, -3, and -4, as well as colony stimulating factors such as G-CSF, GM-CSF, and M-CSF. Recently, one group has utilized IL-2 to stimulate peripheral blood cells in order to expand and produce large quantities 35 of cells which are cytotoxic to tumor cells (Rosenberg et al., *N. Engl. J. Med.* 313:1485-1492, 1985).

35 **[0006]** Others have suggested the use of antibodies in the treatment of cancer. Briefly, antibodies may be developed which recognize certain cell surface antigens that are either unique, or more prevalent on cancer cells compared to normal cells. These antibodies, or "magic bullets," may be utilized either alone or conjugated with a toxin in order to 40 specifically target and kill tumor cells (Dillman, "Antibody Therapy," *Principles of Cancer Biotherapy*, Oldham (ed.), Raven Press, Ltd., New York, 1987). However, one difficulty is that most monoclonal antibodies are of murine origin, and thus hypersensitivity against the murine antibody may limit its efficacy, particularly after repeated therapies. Common side effects include fever, sweats and chills, skin rashes, arthritis, and nerve palsies.

40 **[0007]** One additional difficulty of present methods is that local recurrence and local disease control remains a major challenge in the treatment of malignancy. In particular, a total of 630,000 patients annually (in the U.S.) have localized disease (no evidence of distant metastatic spread) at the time of presentation; this represents 64% of all those patients diagnosed with malignancy (this does not include nonmelanoma skin cancer or carcinoma *in situ*). For the vast majority of these patients, surgical resection of the disease represents the greatest chance for a cure and indeed 428,000 will be cured after the initial treatment - 428,000. Unfortunately, 202,000 (or 32% of all patients with localized disease) will 45 relapse after the initial treatment. Of those who relapse, the number who will relapse due to local recurrence of the disease amounts to 133,000 patients annually (or 21% of all those with localized disease). The number who will relapse due to distant metastases of the disease is 68,000 patients annually (11% of all those with localized disease). Another 102,139 patients annually will die as a direct result of an inability to control the local growth of the disease.

50 **[0008]** Nowhere is this problem more evident than in breast cancer, which affects 186,000 women annually in the U.S. and whose mortality rate has remained unchanged for 50 years. Surgical resection of the disease through radical mastectomy, modified radical mastectomy, or lumpectomy remains the mainstay of treatment for this condition. Unfortunately, 39% of those treated with lumpectomy alone will develop a local recurrence of the disease, and surprisingly, so will 25% of those in which the resection margin is found to be clear of tumor histologically. As many as 90% of these local recurrences will occur within 2 cm of the previous excision site.

55 **[0009]** Similarly, in 1991, over 113,000 deaths and 238,600 new cases of liver metastasis were reported in North America alone. The mean survival time for patients with liver metastases is only 6.6 months once liver lesions have developed. Non-surgical treatment for hepatic metastases include systemic chemotherapy, radiation, chemoembolization, hepatic arterial chemotherapy, and intraarterial radiation. However, despite evidence that such treatments can

transiently decrease the size of the hepatic lesions (e.g., systemic chemotherapy and hepatic arterial chemotherapy initially reduces lesions in 15-20%, and 80% of patients, respectively), the lesions invariably reoccur. Surgical resection of liver metastases represents the only possibility for a cure, but such a procedure is possible in only 5% of patients with metastases, and in only 15-20% of patients with primary hepatic cancer.

5 [0010] One method that has been attempted for the treatment of tumors with limited success is therapeutic embolization. Briefly, blood vessels which nourish a tumor are deliberately blocked by injection of an embolic material into the vessels. A variety of materials have been attempted in this regard, including autologous substances such as fat, blood clot, and chopped muscle fragments, as well as artificial materials such as wool, cotton, steel balls, plastic or glass beads, tantalum powder, silicone compounds, radioactive particles, sterile absorbable gelatin sponge (Sternispon, Gelfoam), oxidized cellulose (Oxyceel), steel coils, alcohol, lyophilized human dura mater (Lyodura), microfibrillar collagen (Avitene), collagen fibrils (Tachotop), polyvinyl alcohol sponge (PVA; Ivalon), Barium-impregnated silicon spheres (Biss) and detachable balloons. The size of liver metastases may be temporarily decreased utilizing such methods, but tumors typically respond by causing the growth of new blood vessels into the tumor.

10 [0011] A related problem to tumor formation is the development of cancerous blockages which inhibit the flow of material through body passageways, such as the bile ducts, trachea, esophagus, vasculature and urethra. One device, the stent, has been developed in order to hold open passageways which have been blocked by tumors or other substances. Representative examples of common stents include the Wallstent, Strecker stent, Gianturco stent and the Palmaz stent. The major problem with stents, however, is that they do not prevent the ingrowth of tumor or inflammatory material through the interstices of the stent. If this material reaches the inside of a stent and compromises the stent lumen, it may result in blockage of the body passageway into which it has been inserted. In addition, presence of a stent in the body may induce reactive or inflammatory tissue (e.g., blood vessels, fibroblasts, white blood cells) to enter the stent lumen, resulting in partial or complete closure of the stent.

15 [0012] The present invention provides compositions and methods suitable for treating cancers and other angiogenesis-dependent diseases which address the problems associated with the procedures discussed above, and further provides other related advantages.

Summary of the Invention

20 [0013] Briefly stated, the present invention provides anti-angiogenic compositions, as well as methods and devices which utilize such compositions for the treatment of cancer and other angiogenesis-dependent diseases. Within one aspect of the present invention, compositions are provided (hereinafter referred to as "anti-angiogenic compositions") comprising (a) an anti-angiogenic factor and (b) a polymeric carrier. A wide variety of molecules may be utilized within the scope of the present invention as anti-angiogenic factors, including for example Anti-Invasive Factor, retinoic acids and their derivatives, taxol, taxol analogues and taxol derivatives, and members of the group consisting of Suramin, 25 Tissue Inhibitor of Metalloproteinase-1, Tissue Inhibitor of Metalloproteinase-2, Plasminogen Activator Inhibitor-1 and Plasminogen Activator Inhibitor-2. Similarly, a wide variety of polymeric carriers may be utilized, representative examples of which include poly(ethylene-vinyl acetate) crosslinked with 40% vinyl acetate, poly (lactic-co-glycolic acid), polycaprolactone polylactic acid, copolymers of poly(ethylene-vinyl acetate) crosslinked with 40% vinyl acetate and polylactic acid, and copolymers of polylactic acid and polycaprolactone. Within one embodiment of the invention, the composition has 30 an average size of 15 to 200 μm .

35 [0014] Within another aspect of the present invention methods for embolizing a blood vessel are provided, comprising the step of delivering into the vessel a therapeutically effective amount of an anti-angiogenic composition (as described above), such that the blood vessel is effectively occluded. Within one embodiment, the anti-angiogenic composition is delivered to a blood vessel which nourishes a tumor.

40 [0015] Within yet another aspect of the present invention, stents are provided comprising a generally tubular structure, the surface being coated with one or more anti-angiogenic compositions. Within other aspects of the present invention, methods are provided for expanding the lumen of a body passageway, comprising inserting a stent into the passageway, the stent having a generally tubular structure, the surface of the structure being coated with an anti-angiogenic composition 45 as described above, such that the passageway is expanded. Within various embodiments of the invention, methods are provided for eliminating biliary obstructions, comprising inserting a biliary stent into a biliary passageway; for eliminating urethral obstructions, comprising inserting a urethral stent into a urethra; for eliminating esophageal obstructions, comprising inserting an esophageal stent into an esophagus; and for eliminating tracheal/bronchial obstructions, comprising inserting a tracheal/bronchial stent into the trachea or bronchi. In each of these embodiments, the stent has a generally 50 tubular structure, the surface of which is coated with an anti-angiogenic composition as described above.

55 [0016] Within another aspect of the present invention, methods are provided for treating tumor excision sites, comprising administering an anti-angiogenic composition as described above to the resection margins of a tumor subsequent to excision, such that the local recurrence of cancer and the formation of new blood vessels at the site is inhibited. Within yet another aspect of the invention, methods for treating corneal neovascularization are provided, comprising the step